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Quality of Life in CIDP patients treated with subcutaneous immunoglobulin.

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CONFLICTS OF INTEREST

Anne-Kathrine Ryltoft has no conflicts of interest

Ali Al-Zuhairy has received research support from Shire

Søren Hein Sindrup has no conflicts of interest

Henning Andersen has received research and travel support from Octapharma, CSL Behring and Genzyme/Sanofi, speaker honoraria from Genzyme/Sanofi; NOVO and Alexion and served as consultant on advisory board of UCB Pharma, NMD Pharma and Genzyme/Sanofi.

Lars Kjøbsted Markvardsen has received speaker honoraria from Octapharma, CSL Behring and Alexion.

DATA VALUE STATEMENT

The corresponding author have access to all data published

ABSTRACT

Background: Subcutaneous immunoglobulin (SCIG) is effective treatment of chronic inflammatory demyelinating polyneuropathy (CIDP). Quality of Life (QoL) increases following switch from intravenous administration to SCIG, but its correlation to clinical functioning is sparsely studied.

Aims of the study: The aim of this study is to evaluate the correlation of QoL and clinical functioning in CIDP patients treated with SCIG.

Methods: Danish patients with CIDP with a disease duration <10 years and currently treated with SCIG were eligible for inclusion. QoL was assessed with EQ-5D-5L and disability by the overall disability sum score (ODSS) and rasch built overall disability score (RODS). Gait performance was evaluated by a 40-meter-walk test (40-MWT) and a 6-spot-step test (6-SST) along with assessment of muscle strength (Medical Research Council score (MRC)). Correlations between QoL and the measured scores were calculated.

Results: Of 92 eligible patients 44 were included. QoL on the visual analogue scale (VAS) was 65% (range: 15-90) of the level of healthy controls ($p=0.03$) and correlated to impaired gait function by 40-MWT and 6-SST. QoL correlated to RODS and ODSS whereas there was no correlation to the MRC-score.

Conclusions: In SCIG treated CIDP patients QoL is reduced and correlates to gait performance and disability.

KEY WORDS CIDP, subcutaneous immunoglobulin, Quality of Life

1. INTRODUCTION

Subcutaneous immunoglobulin (SCIG) is effective as maintenance treatment in chronic inflammatory demyelinating polyneuropathy (CIDP) in short and longterm (1-4). Quality of Life (QoL) and treatment satisfaction are high in patients treated with SCIG (4, 5) and home-based treatment seems flexible and convenient (6, 7).

Previous studies of QoL in CIDP have reported that physical health is affected more than mental health (8), and that QoL improves during treatment with immunoglobulin (5, 9).

Correlation of QoL to clinical performance (e.g. disability, muscle strength, sensory disturbances, severity of pain and electrophysiology) have been demonstrated in several studies of CIDP, with only one study evaluating a selective cohort of SCIG treated patients (8-12). The relation between gait performance and QoL is not described.

In Denmark, SCIG is the preferred treatment for CIDP, however it remains unknown how QoL changes during longterm treatment and how this relates to clinical characteristics.

The aim of our study was to address whether and how QoL relates to disability and clinical performance in a nationwide cohort of CIDP patients on long-term SCIG treatment.

2. MATERIALS AND METHODS

The study is a nation-wide, cross-sectional study of CIDP patients treated with SCIG. Approximately 120 patients in Denmark are treated with SCIG. Patients were identified from all four neurological departments responsible for treatment of all Danish CIDP patients. Inclusion criteria were a diagnosis of CIDP after January 2007, age 18-90 years, and current treatment with SCIG. All patients have prior to SCIG been treated with IVIG as maintenance treatment. In 2010 SCIG was introduced in Denmark and consequently in patients diagnosed after 2007 the majority of immunoglobulin will have been administered subcutaneously. There were no exclusion criteria.

The study was approved by the Ethics Committee (1-10-72-233-16) and participants gave informed consent.

Quality of Life (QoL) was evaluated with the EQ-5D-5L questionnaire including the visual analogue scale (VAS) and compared to Danish normative values (13). EQ-5D-5L has five dimensions: (1) mobility, (2) usual activities, (3) self-care, (4) pain/discomfort and (5) depression/anxiety. The patient rates the impact on each dimension from none to mild, moderate, severe or unable, and eventually an index value is calculated. Moreover, patients rate their health ranging from 0 (worst health) to 100 (best health) on a VAS.

Disability was assessed using the Overall Disability Sum Score (ODSS) and the Rasch-built Overall Disability Scale (RODS) (14). Walking performance was assessed with a 40-meter-walk test (40-MWT) and the 6-spot-step test (6-SST) (15, 16). At the 6-SST test gait and balance is evaluated. In a lane of 5x1 meter five blocks are placed as follows: two on the right side, two on the left side and one in the middle at the end. The blocks should be kicked sideways only using either the right or left leg as fast as possible. A double-determination was measured with calculation of the average value.

A modified MRC-score was applied including shoulder abduction, elbow flexion/extension, wrist flexion/extension, hip flexion, knee flexion/extension and ankle dorsal flexion. Finally, grip strength was measured using a handheld JAMAR dynamometer and expressed as the average of a bilateral triple-determination (17). Dexterity was evaluated with the 9-peg-hole test (9-PHT) using the average value of bilateral double-examinations (18).

Data are presented as means (95% CI) or medians (range: min-max). Data were analysed with Student's t-tests or Wilcoxon rank-sum test. Pearson's or Spearman's analyses were used to detect correlations and the interpretation using the following: <0.25 = no/little correlation; $0.25-0.50$ = fair correlation; $0.51-0.75$ = moderate correlation; >0.75 = good/excellent correlation.

Bonferroni correction was performed to adjust for multiple comparisons with a p-value < 0.002 ($0.05/25$ comparisons).

3. RESULTS

Ninety-two patients were eligible for inclusion, the remaining 28 were treated with SCIG for other reasons than CIDP or had been treated with SCIG for more than 10 years. Thirty-nine patients declined to participate (81%) and nine were no longer treated with SCIG (19%) resulting in 44 patients evaluated. The characteristics of the participants are presented in Table 1. Non-participating patients did not differ according to age, gender, duration of CIDP or duration of SCIG treatment.

Median EQ-5D-5L-VAS was 65% (range: 15-90) of a possible maximum of 100% ($p=0.03$), whereas EQ-5D-5L-index value was 0.7 (range: 0.4-1.0) ($p<0.0001$) with the most impaired dimensions being *pain/discomfort* (82%), *usual activities* (77%) and *mobility* (75%). The median ODSS was 2 points (range: 0-7) whereas the median score on the RODS was 40 points (range: 21-48).

Compared to normative values the MRC-score, grip strength and time to perform the 9-PHT, 40-MWT and 6-SST were all reduced (Table 2).

EQ-5D-5L-VAS had a fair correlation to ODSS and moderate to RODS, 40-MWT and 6-SST ($p<0.002$). In contrast there was no correlation to muscle strength (MRC) or grip strength. EQ-5D-5L-index value correlated to ODSS and RODS ($p<0.002$), 40-MWT ($p=0.015$) and 6-SST ($p=0.0095$) (Table 3). EQ-5D-5L-VAS and EQ-5D-5L-index value correlated moderately ($r=0.72$; $n=44$; $p<0.0001$).

EQ-5D-5L-VAS and index value did not correlate to age, gender, duration of CIDP or duration of SCIG treatment. ODSS correlated moderately to 40-MWT and 6-SST ($p<0.002$) whereas RODS correlated closely to 40-MWT and moderately to 6-SST ($p<0.002$). Finally, RODS and ODSS correlated to both the 9-PHT and the MRC (Table 3).

4. DISCUSSION

In CIDP patients treated with SCIG for more than five years, QoL correlated to disability and gait performance but not to the MRC-score or grip strength.

Previous studies have described correlations between QoL, muscle strength, sensory deficits, disability, fatigue and electrophysiological findings. Kacar et al described in a cohort of 106 CIDP patients that QoL by Individualized Neuromuscular QoL (IN-QoL) correlated to muscle strength by MRC-score, disability and fatigue. However, the correlation to MRC and disability was weak with r -values of 0.19 to 0.25 (10). Bozovic et al used short form 36 (SF-36) and demonstrated a fair correlation to sensory score and moderate score to disability and MRC-score (8). Okhovat et al demonstrated that the physical domain in SF-36 correlates to muscle strength of hip, ankle and hand (12). Our

findings confirmed a moderate correlation between QoL and disability, but could not demonstrate a correlation to MRC although the r-value was comparable (10). Different QoL scales are used, and therefore they cannot be compared head-to-head. One explanation of the different outcomes could be that IN-QoL and SF-36 are more detailed and include more domains based on a larger number of questions than EQ-5D-5L (43 and 36 vs 5).

CIDP patients often have more weakness in the lower extremities and therefore we expected MRC to correlate with walking performance, however, other factors seem to play a role including sensory deficits. It is noteworthy that our MRC assessment included both upper and lower extremities. Anyhow, our findings suggest that disability rather than muscle strength affects QoL. This was confirmed by Cirillo et al who reported that sensory action potentials (SNAP) correlated closely to QoL (11).

Compared to healthy subjects both the EQ-5D-5L VAS and the index value were reduced. QoL improves following IVIG and SCIG treatment in CIDP but did not normalize to the level of healthy subjects, and moreover half of the variance in QoL can be explained by impairment and disability (9, 11). In EQ-5D-5L mild impairment (a score of 2 points) in each of the five dimensions will reduce the calculated index value from 1 to 0.85 and with more than one dimension affected it will lower to approximately 0.75 (19). In CIDP a EQ-5D-5L-VAS of 63% and a EQ-5D-5L-index value of 0.72 seems high as 75% had a score on *mobility* >1 and 77% had a score on *usual activities* >1. The discrepancy between EQ-5D-5L-VAS and EQ-5D-5L-index value may have several explanations, one being that weekly treatment with SCIG has an impact on EQ-5D-5L-VAS although it is less than IVIG (6).

Cirillo et al reported a score on EQ-5D-5L-VAS of 86% (11) which is higher than ours, but the PATH-trial reported a mean score of 67-72%, which is comparable to our findings. Similar to our patients the PATH-cohort were on stable treatment at enrolment and they maintained their VAS during treatment with SCIG in two different doses (0.2 vs 0.4 g/kg/week) with no differences inbetween (5).

Our study was limited by a cross-sectional design and the lack of a control group. As the study had no exclusion criteria comorbidities, possible sub-optimal treatment and inclusion of patients in remission may have influenced our results, especially QoL which is sensitive to other factors than CIDP it self. Further studies are needed including studies on reduction of dosage of immunoglobulin to evaluate the need and effect of long-term treatment with SCIG. Clearly, the Individual Neuromuscular QoL scale (IN-QoL) (10) would have been relevant to include, however this was not published when our study was conducted.

In conclusion, QoL correlates moderately to disability and walking performance, but not to MRC and grip strength in CIDP patients treated with SCIG. Our findings indicate that evaluation of walking performance is crucial in patients with CIDP and we suggest that this should receive more attention in future studies and in the daily practice of CIDP management.

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TABLES

Table 1: Clinical and treatment characteristics.

N	44
Age (years)	61 (30 to 85)
Gender (M/F)	37 (84) / 7 (16)
Body Mass Index (kg/m²)	26.0 (18.9 to 35.8)
Disease duration (months)	37 (12 to 106)
Duration of IVIG prior to SCIG (months)	8.3 (2.3 to 63.4)
Dose of initial IVIG (g/week)*	24.5 (10 to 50) n=38
Duration of SCIG treatment (months)	30 (5.3 to 96.0)
Current SCIG dose (g/week)	29.7 (5.0 to 69.3)
Current change in SCIG dose from initiation (%)	0 (-57.0 to 61.5)
Supplementary IVIG**	9 (20.5)

Values are median (range) or numbers (%)

*Data not available from patient files for all patients

**Additional treatment with IVIG during SCIG treatment. Reasons included worsening of symptoms, poor compliance and accelerated treatment prior to holiday abroad and surgery.

Table 2: Medical Research Council score (MRC), grip strength, 9-peg-hole test (9-PHT), 6-spot-step test (6-SST) and 40-meter-walk test (40-MWT).

	Absolute value	Pct. of expected	P-value
MRC (n=44)	88.3 points (70.5 – 90.0)	98.1 % (78.3 – 100.0)	<0.0001
Grip strength (n=43)	32.7 kg (12.0 – 70.7)	86.2 % (33.6 – 149.8)	0.0053
9-PHT (n=44)	24.5 sec (15.4 – 103)	80.8 % (-197.6 – 118.5)	0.0005
6-SST (n=42)	7.7 sec (4.1 – 18.3)	Na	Na
40-MWT (n=41)	25.8 sec (13.8 – 59.1)	80.1 % (35.4 – 125.1)	<0.0001

Median and range (min to max). Na = not available

P-values refer to comparison between “Pct. of expected” and the value 100 by one-sample t-test or Wilcoxon signed rank test.

Table 3: Correlations between muscle strength, disability, quality of life and functional tests.

	RODS	ODSS	EQ-5D-5L VAS	EQ-5D-5L index
RODS	-	$r_s(43) = -0.82^*$	$r_p(43) = 0.68^*$	$r_p(43) = 0.73^*$
ODSS	$r_s(43) = -0.82^*$	-	$r_p(44) = -0.48^*$	$r_p(44) = -0.49^*$
Grip strength	$r_p(43) = 0.26$	$r_s(43) = -0.50^*$	$r_s(43) = 0.056$	$r_p(43) = 0.10$
MRC	$r_s(44) = 0.62^*$	$r_s(44) = -0.70^*$	$r_s(44) = 0.22$	$r_s(44) = 0.27$
9-PHT	$r_s(43) = -0.60^*$	$r_s(44) = 0.67^*$	$r_s(44) = -0.28$	$r_s(44) = -0.22$
40-MWT	$r_s(42) = -0.80^*$	$r_s(43) = 0.72^*$	$r_s(43) = -0.56^*$	$r_s(43) = -0.37$
6-SST	$r_s(41) = -0.72^*$	$r_s(42) = 0.67^*$	$r_s(42) = -0.58^*$	$r_s(42) = -0.40$

* $p < 0.002$ (Bonferroni corrected significance level)

cIKS=Combined isokinetic muscle strength; RODS=rasch-built overall disability scale; ODSS=overall disability sum score; VAS=visual analogue scale; MRC=medical research council score; 9-PHT=9 peg hole test; 40-MWT=40 meter walking test; 6-SST=6 spot step test; r_p (degrees of freedom)=pearson correlation coefficient; r_s (degrees of freedom)=spearman rank correlation coefficient